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(54) Kaugummi zur Mund- und Rachendesinfektion, sowie Verfahren zu seiner Herstellung.

(57) 0.05 bis 0.8 Gewichtsteile eines Mund- und oder Rachendesinfiziens liegen in oder an einer Matrix, die 100 Gewichtsteile Kaugummibase enthält, und oder in einer die Matrix umhüllenden Drageeschicht vor. Eine solche pharmazeutische Zubereitung dient u.a. der Verhinderung der Plaque-Bildung. Als Desinfektionsmittel kommt insbesondere Cetylpyridiniumchlorid in Frage. In der Matrix liegen vorzugsweise ausserdem 2 bis 15 Gewichtsteile einer lipoiden Substanz und oder 5 bis 20 Gewichtsteile eines Sprengmittels vor, auf dem bevorzugt das Desinfektionsmittel aufgebracht bzw. verteilt ist. Zur Herstellung dieses Kaugummis wird gemahlene Kaugummibase mit Pulverteilchen wenigstens eines Zuschlagstoffes, die mit Fetten und/oder Wachsen überzogen sind, unter Kühlung gemischt. Der Mischung und oder einer sie überziehenden Drageeschicht werden 0.05 bis 0.8 Gewichtsteile eines Desinfektionsmittels zugesetzt. Anschliessend wird in gekühlten Vorrichtungen zu Tabletten verpresst.

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[54] Title: **CHEWING GUM FOR DISINFECTION OF THE MOUTH AND THROAT AND PROCESS FOR ITS PRODUCTION**

Abstract

0.05-0.8 part by weight of a mouth and throat disinfectant is present in or on a matrix containing 100 parts by weight of a chewing gum base, and/or in a sugar coating surrounding the matrix. A pharmaceutical preparation of this type serves, among other things, to prevent the formation of plaque. A suitable disinfectant is cetylpyridinium chloride. Also present in the matrix are preferably 2-15 parts by weight of a lipoid substance and/or 5-20 parts by weight of a disintegration agent, on which preferably the disinfectant is applied or distributed. To produce this chewing gum, ground chewing gum base is mixed under refrigeration with powder particles of at least one additive which are coated with fats and/or waxes. 0.05-0.8 part by weight of a disinfectant is added to the mixture and/or to the sugar coating surrounding it. Finally, tablets are pressed in cooled equipment.

CHEWING GUM FOR DISINFECTION OF THE MOUTH AND THROAT AND PROCESS FOR ITS PRODUCTION

The invention pertains to a chewing gum in accordance with the preamble of Claim 1. Heretofore, essentially the use of solutions for gargling or spraying and lozenges loaded with suitable active agents has been proposed for the disinfection of the mouth and throat areas in grippal infections and other illnesses caused by viruses or bacteria such as cocci (*Deutsche Apothekenzeitung*, October 16, 1989, p. 2281 ff.). During gargling, the active agents reach only the anterior portion of the oral cavity and that only for a short time; because the gargling solution is highly concentrated, it is recommended that it not be swallowed. As a result, the tonsils and throat receive little treatment. Spray solutions are therefore better, but these too act for only a short time. Lozenges make it possible to prolong the duration of the action, but even in this case the activity lasts for only a few minutes; it is never possible to exclude the possibility that the lozenge will be chewed and swallowed—especially in the case of children. High concentrations of cetylpyridinium chloride (CPC) as well as of other active agents can lead to lesions of the mucosa. This can occur when the tablets—as is usually the case with lozenges—rest directly on the mucous membranes. The saliva which has become loaded with the active agent makes little or no contact with the plaque coating on the teeth, which is a preferred medium for the growth of bacteria.

All these formulations are also used in inflammations of the tonsils, which exercise a defensive function against infections but which also serve as the entryways for microorganisms and toxins into the circulatory system. Thus, 10^7-10^9 microorganisms are present per mL of saliva or 10^{11}-10^{12}

microorganisms per gram of plaque. In most cases, the change in the defensive status as a result of viral infections is the precondition for the development of an acute disease, which is often followed by a secondary bacterial infection. Disinfectants such as 8-hydroxyquinoline, 2,4-dichlorobenzyl alcohol, cresols, povidone-iodine, hexetidine, hexamidine, chlorhexidine, and quaternary ammonium compounds, especially cetylpyridinium chloride, benzalkonium chloride, and dequalinium chloride, are used as antiseptics for the areas of the mouth and throat. Local antibiotics such as bacitracin and tyrothricin are used to disinfect the throat. In a concentration of 0.05%, cetylpyridinium chloride inhibits *in vitro* the growth of *Streptococcus pyrogenes*, *Streptococcus aureus*, and *Candida albicans* within a period of 30 seconds. α-Hemolytic streptococci and the above-mentioned *Streptococcus aureus* and *Streptococcus pyrogenes* are also reduced by 80-90% *in vivo*. Cetylpyridinium chloride also prevents the formation of dental plaque. A study with artificial dental plaque of *Streptococcus mutans* showed that disinfection with 0.1% cetylpyridinium chloride solution reduced the formation of acid by microorganisms. In a preliminary memorandum, a dose of 0.025-0.1% for a rinse and for lozenges is recommended by the American Federal Health Agency (FDA) for adults and children over 3. There are numerous cetylpyridinium chloride tablets available in dosages of 0.5-2.5 mg per individual dose in addition to the disinfecting sprays and gargles. In the U.S. Pharmacopoeia, for example, there is a monograph on cetylpyridinium pastilles.

To avoid these disadvantages, it has therefore already been proposed that the disinfectant be incorporated into a chewing gum (FR-A-23 20083, 1977; US-

old) proposal, with the result that it has not been possible to implement it so far.

In the conventional process for the production of chewing gum normally used in the food industry, the active agent is kneaded into the chewing gum base and thus fully incorporated. In the case of cetylpyridinium chloride (CPC), however, we are dealing with an extremely nonpolar substance with very good solubility in fats. The long-chain cetyl group of the molecule in particular is very similar to a fat and can also be emulsified easily. When CPC is kneaded into a chewing gum composition with a high percentage of fatty components, the release of the active component is sharply reduced to, for example, a maximum of 20% within a chewing time of 15-30 minutes. The French patent even states that the active agent is not released until after 15 minutes. The desired disinfection of the mouth and throat areas, however, is therefore not possible in this way.

The invention is therefore based on the task of creating a chewing gum for disinfecting the mouth and throat which does not suffer from the disadvantages of the conventional preparations discussed above. The surprising manner in which this task is accomplished is described by the features of the characterizing portion of Claim 1. Advantageous embodiments of the invention and a process for the production of the chewing gum preparations according to the invention are described in the characterizing portions of the subclaims.

The production of chewing gum from granulate is already known from WO-A-8603967; in that publication, 20-40 parts of fats or waxes are required. Large amounts of fats or waxes, however, have a negative effect on the release because of their strongly lipophilic behavior, as already mentioned. In the

case of the lipophilic active agents according to the invention, it is possible, therefore, to process the granulate mixture into tablets with a fat content of only 2-15%, which later result in formation of the chewing gum during chewing.

This reduction of the lipophilic content leads surprisingly to an increase in the release of the active agent by at least 10% to as much as about 45% of the CPC within 15 minutes; this is still not enough, however, to achieve a disinfecting concentration of the active agent during the first few minutes of chewing. It would be desirable to increase the CPC release during the first 10 minutes to 60-70%.

Increasing the soluble components in the tabletting composition, an idea which is logical in itself, did not lead to the desired increase in the diffusion of CPC from the chewing gum matrix. The release of the active agent can be improved, surprisingly, by the addition of at least one of the substances cited in Claim 3. Crosslinked polyvinylpyrrolidone is normally used in the production of tablets as a disintegration agent to improve the disintegration time. It is therefore surprising that the addition of one part of crosslinked polyvinylpyrrolidone to the chewing gum according to the invention leads not to the expected improvement in the disintegration behavior but rather primarily to an improvement in the diffusion of the active agent CPC through and out of the chewing gum matrix. This is especially true when, as will be explained further below, the active agent is applied throughout the substance. This improves the release behavior and in particular ensures the highly uniform, continuous release of the active agent during chewing. This improvement in the diffusion from a chewing gum matrix leads to the result that, in the first minute, an initial CPC dose of about 25-30% is released;

after 3 minutes, a dose of about 40% is obtained; and after 10 minutes, the total dose released reaches about 60%. That is, the amount of released CPC with respect to the base formulation is increased again by at least 50%. After an initial dose of about 0.5-0.6 mg, CPC is released continuously from the chewing gum according to the invention over a period of 15 minutes, and thus a disinfecting solution with an appropriate active agent concentration is obtained.

In DE-A1 29 22670; a chewing gum has been proposed in which active agents are to be introduced in such a way that they are incorporated into porous particles of materials such as aluminum hydroxide, aluminum oxide, cellulose-containing skeleton compounds, calcium carbonate, etc. As mentioned at the beginning, however, these chewing gums were unacceptable either because of technical production difficulties or because of the impossibility of ensuring the satisfactory release of the active agent. The substances proposed in accordance with the invention, however, improve the diffusion of the disinfectants from the chewing gum into the saliva.

In the chewing gum according to the invention, the active agent in the therapeutic system is present in incorporated form. As a result of the uniform release of the active agent over a period of about 10 minutes, the therapeutically relevant (and not excessive) active agent concentrations are formed with saliva in such a way that the risk of microlesions is reduced.

It is intended in particular that the chewing gum according to the invention be used as a preventive agent against caries and gingivitis. It is known that cetylpyridinium chloride reduces dental plaque. When the active agent-containing chewing gum is chewed, disinfecting active agent concentrations are applied directly to the teeth and gums, and simultaneously,

a mechanical action is exerted against the plaque. Only in this way can the desired therapeutic result be achieved. Therefore, the reduction of dental plaque in this way is more favorable than that which can be achieved with conventional lozenges.

It is also possible, however, to use to advantage in the chewing gum according to the invention, dequalinium chloride (which has a somewhat bitter taste, however), tyrothricin (which requires special measures to process), and benzalkonium chloride, the latter especially in mixtures with CPC.

The active agent matrix is prepared, for example, by applying a preferably alcoholic solution of the active agent to 20-60% of the proposed substance. The substance is placed in a force-feed mixer, wetted with the alcoholic solution of the active agent, mixed to homogeneity, and then dried.

This method of applying the active agent to the substance is effective in achieving the desired result of improving the release behavior and also has an advantageous effect on its uniform distribution.

The production process is similar to that described in PCT/EP85/00735.

100 parts of commercial chewing gum base, consisting of latex and commercial additives, which are supplied in the form of plates, are cooled to -10°C , broken up, ground in a cooled mill to a particle size of 0.4-0.8 mm, and stored in tightly sealed polyethylene containers at 0°C.

5 parts of fatty acid triglyceride are melted over a water bath and added to a preheated mixture of 90 parts of lactose and 26 parts of sorbitol. In addition to the additives lactose and sorbitol listed in the above examples, it is also possible to use other additives such as sugar, glucose, fructose, mannitol, maltodextrin, and dextrins, although it is obvious that a cetylpyridinium chloride chewing gum should preferably be sugar-free. It is

well mixed while hot and then stirred to cool it to 0°C with cooling brine. While in the cooled state, the composition is ground to a particle size of 0.2-0.5 mm and then stored at 0°C.

Example 1. Tablet cores.

	I	II	III	IV	V
Gum base	100	100	100	100	100
Fatty acid triglyceride	5	2	8	5	2
Lactose	90	56	100	80	56
Sorbitol	26	63	13.2	36.35	63
Crosslinked PVP	10	10	10	15	10
Starch	5		5		
Cetylpyridinium chloride	0.4	0.4			
Benzalkonium chloride			0.1		
Dequalinium chloride				0.05	
Tyrothricin					0.4
Talcum	5	10	5	5	10
Magnesium stearate	5	5	5	5	5
Flavoring	12	12	12	12	12
Sweetener	1.6	1.6			

	VI	VII	VIII
Gum base	100	100	100
Fatty acid Triglyceride	5	5	5
Lactose	65.4	56	51
Sorbitol	26	50	40
Talcum	10	8	10
Magnesium stearate	—	4	5
Flavoring	12	12	12
Sweetener	1.6	3.0	1.6
Active agent matrix	40	22.0	35.5

Example 2. Active agent matrix.

	I	II	III	IV
Tyrothricin	1.0			
Cetylpyridinium chloride		1.0	2.0	
Benzalkonium chloride		1.0		
Dequalinium chloride				0.5
Avicel (microcrystalline cellulose)	20			
Sodium alginate	19			
Na carboxymethylcellulose				35
Crosslinked PVP		20	20	

0.4 part of cetylpyridinium chloride is dissolved in 4 parts of ethanol and stirred into a homogeneous mixture of 10 parts of a disintegration agent, preferably, for example, crosslinked polyvinylpyrrolidone, and 5 parts of starch to form a homogeneous mixture. In addition to the compounds cited in Example 2, it is also possible to use pectins, formaldehyde-casein products, and hardened castor oil as disintegration agents. It is also possible to incorporate the cetylpyridinium chloride into a fat or oil phase. Thereupon, the composition is dried under vacuum at 60°C. The resulting powder mixture is pressed through a screen with a mesh width of 0.2 mm. The production of the other active agent matrices is carried out in a manner similar to that used for the compositions according to Example 2.

The granulated gum base and fat base are transferred to a vacuum mixer, which is cooled with brine to 5°C; then solid flavorings, sweeteners, and, for example, 15 parts of the active agent matrix are added. The mixer is evacuated to exclude the influence of humid air and the danger of its condensation, and the composition is mixed as the vacuum mixing vessel is raised and turned. Then air is allowed to enter, which may be at a maximum relative humidity of 10%, and the finished mixture is discharged via a rotating screen into storage containers, which are also stored at -5°C to 0°C.

Another way of incorporating the CPC is to sugar-coat the pressed cores. In this case, some of the CPC (the remaining portion of the CPC is then embedded in the matrix substance in the manner described above) or all of it is integrated into the coating composition. By repeated, layer-by-layer pouring or spraying of the CPC-containing suspension solution in a coating pan, which starts out cold and is then progressively heated, a sugar coating of the desired thickness is obtained. The coating process can also be done

without sugar, which obviously is significant for a product which can be used to prevent the formation of dental plaque.

The compound is preferably pressed into tablets in cooled tabletting machines.

Claims

1. Chewing gum containing 0.05-0.8 part by weight of a mouth and/or throat disinfectant per 100 parts by weight of a chewing gum base and/or in a sugar coating surrounding the base, characterized in that the chewing gum base is present in the form of a granulate and in mixture with 2-15, preferably 5-10 parts by weight, of at least one lipoid substance, preferably di- and triglycerides of fatty acids, high-viscosity oils, waxes, or paraffin oil.

2. Preparation according to Claim 1, characterized in that the mixture contains, as disinfectant, at least one of the following compounds: cetylpyridinium chloride, benzalkonium chloride, dequalinium chloride, and tyrothricin.

3. Preparation according to Claim 1 or Claim 2, characterized in that the mixture also contains 5-20, preferably 10-15, parts by weight of at least one of the following substances: crosslinked polyvinylpyrrolidone, formaldehyde-casein products, and hardened castor oil.

4. Preparation according to one of the preceding claims, characterized in that it also contains sugar-free additives.

5. Process for the production of a preparation according to one of the preceding claims, characterized in that 100 parts by weight of a chewing gum base—preferably ground to a particle size of 0.2-1.0 mm—are mixed under cooling with 100-150, preferably 115-130, parts by weight of powder particles of a least one additive coated with fats and/or waxes, 0.05-0.8 part by weight

of a disinfectant being added to the mixture and/or to a sugar coating, whereupon tablets are pressed in cooled equipment.

6. Process according to Claim 5 for the production of a preparation according to Claim 3, characterized in that the active agent is applied to the substance, which is then mixed with the granulated chewing gum base and pressed into tablets.

7. Process according to Claim 5 or Claim 6, characterized in that the pressing is carried out in cooled equipment.

8. Process according to one of Claims 5-7 for the production of tablets with a sugar coating, characterized in that the tablets are coated with the sugar coating, preferably in several layers, during which process they are heated slowly to a temperature of 35-60°C over a period of, for example, 10-20 minutes, whereupon they are cooled again.

European Patent Office Application No.: EP 90 10 9730

European Search Report

Documents considered to be pertinent			
Category	Name of document with indication of pertinent parts, as needed	Claims concerned	Classification of the application (Int. Cl.)
Y	AT-B- 350 728 (GERGELY) *All*	1,2,4	A 61 K 9/68
Y,D	FR-A-2 320 083 (SIGMA-TAN INDUSTRIE FARMACEUTICHE RIUNITE) *All*	1,2,4	
D,A	DE-A-2 922 670 (BATTELLE-INSTITUT) *All*	6	
D,A	WO-A-8 603 967 (GERGELY) *All*	5,7,8	
D,A	US-A-1 396 641 (KING et al)		
A	GB-A-2 181 646 (MORRIS) *All*	1,5	
			Technical field searched (Int. Cl.[5])
			A 61 K
The present search report was drafted for all claims			
Site of the search: DEN HAAG	Date search completed: 08-27-1990	Reviewer: BENZ K.F.	

Category of documents cited:

X: Particularly pertinent in itself
Y: Particularly pertinent in combination with another document of the same category
A: Technological backgrounds
O: Unwritten disclosure
P: Intercalary document
T: Theory or principle on which the invention is based
E: Prior patent document published on or after the application date
D: Cited in the application
L: Cited for other reasons

&: Member of the same family, corresponding document

Aufgiessen oder Aufspruhen der CPC-haltigen Suspensionslosung in einem zuerst kalten Drageekessel bei anschliessender schrittweiser Erwarmung wird eine Drageedecke von gewunschter Dicke erhalten. Die Dragierung kann auch zuckerfrei erfolgen, was naturlich fur ein Produkt, das gegen die bildung von Zahnplaque eingesetzt werden kann, von Bedeutung ist.

Das Verpressen der Masse erfolgt vorzugsweise in gekuhlten Tablettenmaschinen.

[redacted] B1

1. Chewing gum containing 0.05 to 0.8 parts by weight of an oral and/or pharyngeal disinfectant - in particular a nonpolar or poorly water-soluble one - per 100 parts by weight of chewing gum base and/or in a tablet coat surrounding said base, characterised in that the chewing gum base is present in the form of granules and as a mixture with 2 to 10, preferably 5 to 10, parts by weight of at least one lipoid substance, preferably of di- and triglycerides of fatty acids, relatively highly viscous oil, waxes or liquid paraffin.
2. Chewing gum according to Claim 1, characterised in that at least one if the following compounds is present as a disinfectant: cetylpyridinium chloride, benzalkonium chloride, dequalinium chloride or tyrotricin.
3. Chewing gum according to Claim 1 or 2, characterised in that it furthermore contains 5 to 20, preferably 10 to 15, parts by weight of at least one of the following substances: crosslinked polyvinylpyrrolidone, formaldehyde/casein products or hydrogenated castor oil.
4. Chewing gum according to any of the preceding Claims, characterised in that it furthermore contains sugar-free additives.
5. Process for the preparation of a chewing gum according to any of the preceding Claims, characterised in that 100 parts by weight of a milled chewing gum base - preferably one milled to a particle size of 0.2 to 1.0 mm - are mixed, with cooling, with 100 to 150, preferably 115 to 130, parts by weight of powder particles of at least one additive which has been coated with 2 to 10, preferably 5 to 10, parts by weight of fat and/or wax, 0.05 to 0.8 part by weight of a disinfectant also being added to the mixture and/or a tablet coat and pressing to give tablets being effected in cooled apparatuses.
6. Process according to Claim 5, for the preparation of a formulation according to Claim 3, characterised in that the active ingredient is applied to the substance which is subsequently mixed with the granulated chewing gum base and pressed to give tablets.
7. Process according to Claim 5 or 6, characterised in that compression is effected in cooled apparatuses.
8. Process according to any of Claims 5 to 7 for the preparation of tablets having a tablet coat, characterised in that the tablets are coated with the tablet coat, preferably in several layers, slowly heated to a temperature of 35 to 60(degree)C, for example in the course of 10 to 20 minutes, and then cooled again.

CLAIMS EP 399479 B1

1. Kaugummi mit einem Gehalt an 0,05 bis 0,8 Gewichtsteilen eines Mund- und/oder Rachendesinfizies auf 100 Gewichtsteile Kaugummibase und/oder in einer diese umhullenden Drageeschicht, dadurch gekennzeichnet, dass die Kaugummibase in Granulatform und in Mischung mit 2 bis 15, vorzugsweise 5 bis 10 Gewichtsteilen wenigstens einer lipoiden Substanz vorliegt, vorzugsweise von Di- und Triglyceriden von Fettsauren, hoher [redacted]

PATENTS SUMMARY

Country : European Patent Office

Patent #: 0,399,479 B Index#: 3435

Inventor: Gerhard Gergely Issue Date: 08/11/93

Assignee: Inventor Date of Application: 05/26/89

Title:

CHEWING GUM FOR DISINFECTION OF THE MOUTH AND THROAT AND PROCESS FOR ITS PRODUCTION

Desc.:

Chewing gum for disinfecting the mouth and throat and the process for making it are claimed. The preferred active agent is cetylpyridinium chloride. The gum is prepared by tabletting using ground base. The tablets may also be coated with a sugar coating containing some of the active agent.

Key Words:

10 CHEWING GUM
20 Anticaries/Antiplaque (Gum)
25 Pharmaceutical
356 Waxes
454 Processing Aids
467 Pharmaceutical Agents
471 Coating Materials
515 Tableting
522 Piece Coating,Macroencapsulation
555 Fast or Slow Release/Long Lasting
574 Health Benefit
600 ORAL HEALTH
601 Anticaries/Antiplaque/Anticalculus
611 Breath Freshening
750 Independent Inventor
802 European Patent Office